Broad-range bacterial PCR and meningitis with a negative Gram's stain

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The recent article in *CMI* by Welinder-Olsson *et al.* [1] adds evidence to support the use of broad-range PCR assays for the diagnosis of community-acquired bacterial meningitis. However, some additional information is needed to put these results into clinical perspective.

First, in the report of a diagnostic study, readers expect to know how the reference status—diseased or non-diseased—was defined. The authors describe 57 patients with bacterial meningitis: (i) 25 patients with bacteria detected by PCR and culture of the cerebrospinal fluid (CSF); (ii) 19 among 26 patients with bacteria detected by PCR, but not by culture of the CSF; (iii) six among 14 patients with bacteria detected by culture, but not by PCR of the CSF; and (iv) seven patients with no bacteria detected by PCR or culture of the CSF, but with clinical and laboratory findings suggestive of bacterial meningitis and a relevant pathogen identified from blood culture. However, the total number of bacterial meningitis cases is stated to be 74. Some details on how the diagnosis was reached in the 17 missing patients would be welcome.

Second, the concordance between CSF culture and CSF bacterial PCR is only moderate, with kappa = 0.34 (95% CI 0.14–0.55). As both tests obviously provide useful diagnostic information, the authors conclude (appropriately) that they complement each other. Nonetheless, the outcome of bacterial meningitis is highly dependent on prompt initiation of antibiotic therapy, i.e., before the results of CSF culture are available. From a clinical point of view, the difficult problem is thus to make a quick diagnosis. In this respect, a Gram's stain of CSF is more useful than the CSF culture, since the results are available without delay. A positive result essentially confirms the diagnosis [2] and guides the choice of an appropriate antibiotic regimen. Since the clinician already has the information needed to act efficiently, bacterial PCR is not very useful in such cases. In contrast, PCR might be very helpful in the case of a CSF with a negative result following Gram's stain. It would therefore be valuable to know the sensitivity and specificity of broad-range bacterial PCR for the subgroup of patients with a negative CSF Gram's stain.

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Reply from Drs Welinder-Olsson, Dotevall and Larsson

We appreciate the comments of Dr Steichen concerning our article about the use of broad-range PCR assays for the diagnosis of community-acquired bacterial meningitis. The strength of this work was the combination of clinical and laboratory data. *All* samples of CSF that were sent to the participating laboratories during the study period and that had CSF leukocyte cell counts $\geq 10 \times 10^6$/L were examined using broad-range PCR. Furthermore, *all* medical records of the patients with CSF pleocytosis were analysed. This approach provided the opportunity to study the usefulness and quality of broad-range PCR of bacterial antigen in the clinical setting. Since the participating laboratories received and cultured almost all CSF tests undertaken in the study area, we consider that the results are as relevant to the clinical setting as can be achieved.

As mentioned by Dr Steichen, the details of 25 + 19 patients with verified community-acquired bacterial meningitis were given in Tables 1 and 2 of our article [1]. Table 3 showed the results for an additional seven patients (with the seventh, a probable case of *Staphylococcus aureus* septicaemia, having symptoms of an early meningitis, which was labelled as a bacterial meningitis). In the text, we commented on another seven patients with positive blood cultures and meningeal inflammation, but without positive CSF cultures or PCR test results. In the medical records of the study patients with CSF pleocytosis, clinical evidence of symptoms and signs of probable bacterial meningitis was found in a further 16 (not 17) patients. Each of these 16 patients had inflammatory CSF and clinical signs in accordance with a diagnosis of bacterial meningitis, and no laboratory findings or clinical signs that supported any non-bacterial cause of CSF inflammation. The CSF results for 13 of these 16 patients showed polymorphonuclear cell counts of $19–1293 \times 10^6$/L (median 256) and

lymphocyte cell counts of 9–268 $\times 10^6$/L (median 56), and low CSF glucose levels and/or increased CSF albumin concentrations. The CSF results were missing for three of these patients. All 16 patients were given intravenous antibiotics as for bacterial meningitis. Most patients in this group were considered to be early cases of bacterial meningitis. We are aware that any of these patients might have had other explanations for their CSF pleocytosis, e.g., viral meningitis. However, since they were all judged, on clinical grounds, to be cases of bacterial meningitis, they were included in order to make the study relevant for clinicians. If only culture-verified cases were included, the apparent sensitivity and specificity of broad-range PCR would be higher, but this would not necessarily be true in the clinical setting.

We also agree with Dr Steichen that a Gram's stain of CSF is an important test for early and rapid aetiological diagnosis of bacterial meningitis. However, we did not have the results of a Gram's stain of CSF for all study patients. A further study is required to address this important question.

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